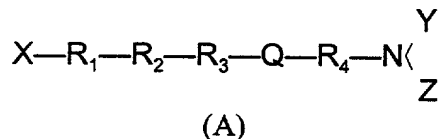


What is claimed is:

1. A compound of having the chemical structure of formula (A):



with peripheral analgesic effect, wherein:

- a) X is selected from the group consisting of H and C₁₋₆ alkyl;
- b) Y and Z are independently selected from the group consisting of H, cyclic aralkyl, and C₁₋₆ alkyl;
- c) R₁ is a tyrosyl residue or a 2',6'-dimethyltyrosyl residue;
- d) R₂ is an amino acid having the R-configuration, aminoisobutyric acid, cyclopropylalanine, cyclohomoleucine or cycloleucine;
- e) R₃ is an aromatic amino acid;
- f) R₄ is an aromatic amino acid residue;
- g) Q is an amide bond or an interposed amide bond mimetic;
- h) with the proviso that when:
- i) R₁ is a tyrosyl residue;
 - ii) R₂ is D-alanine;
 - iii) X, Y, and Z are H; and
 - iv) R₃ is phenylalanine;
- then R₄ is not unsubstituted phenylalanine or phenylalanine substituted with 4NO₂ or 4N₃;
- i) with the further proviso that when:
- i) R₁ is a tyrosyl residue;
 - ii) R₂ is D-alanine;
 - iii) X, Y, and Z are H; and
 - iv) R₄ is phenylalanine;
- then R₃ is not unsubstituted phenylalanine or phenylalanine substituted with 4NO₂;

- j) with the further proviso that when:
- i) R_1 is a tyrosyl residue;
 - ii) R_2 is D-alanine;
 - iii) X, Y, and Z are H; and
 - iv) R_4 is 1'-naphthylalanine;
- then R_3 is not 1'-naphthylalanine or 2'-naphthylalanine;
- k) with the further proviso that when:
- i) R_1 is a tyrosyl residue;
 - ii) R_2 is D-alanine; and
 - iii) X, Y and Z are H,
- then both R_3 and R_4 are not tryptophan;
- l) with the further proviso that when:
- i) R_1 is a tyrosyl residue;
 - ii) R_2 is a D-amino acid with a lower alkyl or lower thioalkyl group as a side chain; and
 - iii) R_4 is a neutral amino acid,
- then R_3 is not unsubstituted phenylalanine;
- m) and wherein said compound is not selected from the group consisting of:
- H-Tyr-D-Phe-Phe-Phe-NH₂;
 - H-Tyr-D-NMePhe-Phe-Phe-NH₂;
 - H-Tyr-D-Tic-Phe-Phe-NH₂;
 - H-Tyr-Pro-Phe-Thr(Bzl)-NH₂;
 - H-Tyr-Pro-Phe-Phe-NH₂;
 - H-Tyr-Pro-Phe-Apb-NH₂;
 - H-Tyr-Pro-Phe-App-NH₂;
 - H-Tyr-Pro-Phe-Aph-NH₂; and
 - H-Tyr-Pro-Apb-Phe-NH₂,

wherein Apb is 2-amino-4-phenylbutanoic acid, App is 2-amino-5-phenylpentanoic acid and Aph is 2-amino-6-phenylhexanoic acid.

30 2. The compound of claim 1, wherein X is H.

3. The compound of either claim 1 or 2, wherein:

- a) R_2 is as defined in claim 1;
b) with the proviso that when:
i) R_1 is a tyrosyl residue;
ii) R_2 is D-alanine; and
iii) Y and Z are H;

then R_3 and R_4 are different and are selected from the group consisting of phenylalanine, and tryptophan.

4. The compound of either claim 1 or claim 2, wherein Q is an amide bond or an interposed amide bond mimetic of the formula Q_1-Q_2 , wherein:

- a) Q_1 is selected from the group consisting of CH_2 , $CHOH$, $C=O$, $C=S$, and $CH=$; and
b) Q_2 is selected from the group consisting of CH_2 , NH , S , SO , SO_2 , O , and $CH=$;
c) with the proviso that when Q_1 is $CH=$, then Q_2 is $CH=$.

5. The compound of claim 3, wherein Q is an amide bond or an interposed amide bond mimetic of the formula Q_1-Q_2 , wherein:

- a) Q_1 is selected from the group consisting of CH_2 , $CHOH$, $C=O$, $C=S$, and $CH=$; and
b) Q_2 is selected from the group consisting of CH_2 , NH , S , SO , SO_2 , O , and $CH=$;
c) with the proviso that when Q_1 is $CH=$, then Q_2 is $CH=$.

6. The compound of claim 5, wherein:

- a) Y and Z are H;
b) R_2 is as defined in claim 1;
c) R_3 is an aromatic amino acid; and
d) R_4 is an aromatic amino acid;
e) with the proviso that when:

i) R_1 is a tyrosyl residue; and

ii) R_2 is D-alanine;

then R_3 and R_4 are different and are selected from the group consisting of phenylalanine and tryptophan.

5 7. The compound of either claim 1 or claim 2, wherein:

a) Y and Z are H;

b) R_2 is as defined in claim 1;

c) R_3 is an aromatic amino acid; and

d) R_4 is an aromatic amino acid;

e) with the proviso that when:

i) R_1 is a tyrosyl residue; and

ii) R_2 is D-alanine;

then R_3 and R_4 are different and are selected from the group consisting of phenylalanine and tryptophan.

10
15 8. The compound of claim 4, wherein:

a) Y and Z are H;

b) R_2 is as defined in claim 1;

c) R_3 is an aromatic amino acid; and

d) R_4 is an aromatic amino acid;

e) with the proviso that when:

i) R_1 is a tyrosyl residue; and

ii) R_2 is D-alanine;

then R_3 and R_4 are different and are selected from the group consisting of phenylalanine and tryptophan.

20
25 9. The compound of claim 6, wherein:

a) R_2 is as defined in claim 1, with the proviso that R_2 is not D-alanine;

b) R_3 is a phenylalanyl residue; and

c) R_4 is a phenylalanyl residue.

10. The compound of claim 7, wherein:
- R_2 is as defined in claim 1, with the proviso that R_2 is not D-alanine;
 - R_3 is a phenylalanyl residue; and
 - R_4 is a phenylalanyl residue.

- 5 11. The compound of claim 8, wherein:
- R_2 is as defined in claim 1, with the proviso that R_2 is not D-alanine;
 - R_3 is a phenylalanyl residue; and
 - R_4 is a phenylalanyl residue.

- 10 12. The compound of claim 6, wherein:
- R_1 is a tyrosyl residue;
 - R_2 is selected from the group consisting of D-serine and D-arginine;
 - R_3 is a phenylalanyl residue;
 - R_4 is a phenylalanyl residue; and
 - Q is an amide bond.

- 15 13. The compound of claim 7, wherein:
- R_1 is a tyrosyl residue;
 - R_2 is selected from the group consisting of D-serine and D-arginine;
 - R_3 is a phenylalanyl residue;
 - R_4 is a phenylalanyl residue; and
 - 20 e) Q is an amide bond.

- 25 14. The compound of claim 8, wherein:
- R_1 is a tyrosyl residue;
 - R_2 is selected from the group consisting of D-serine and D-arginine;
 - R_3 is a phenylalanyl residue;
 - R_4 is a phenylalanyl residue; and
 - e) Q is an amide bond.

15. A compound selected from the group consisting of:

H-Tyr-Aib-Phe-Phe-NH₂;

H-Tyr-D-Nle-Phe-Phe-NH₂;

H-Tyr-D-Ala-Phe-2'-Nal-NH₂;

5 H-Tyr-D-Ala-D-Phe-Phe-NH₂;

H-Tyr-D-Ala-Phe(4NO₂)-Phe(4NO₂)-NH₂;

H-Tyr-D-Ala-Phe-Tic-NH₂;

H-Tyr-D-Ala-Phe-Phe(NMe)-NH₂;

H-Tyr-D-Ala-Phe-1'-Nal-NH₂;

10 H-Tyr-D-Ala-Trp-Phe-NH₂;

H-Tyr-D-Ala-Phe-Trp-NH₂;

H-Tyr-∇Ala-Phe-Phe-NH₂;

∇CH₂-Tyr-D-Ala-Phe-Phe-NH₂;

H-Tyr-D-Nle-Phe-Trp-NH₂;

15 H-Tyr-D-Nle-Phe-2'-Nal-NH₂;

H-Tyr-D-Nle-Trp-Phe-NH₂;

H-Tyr-D-Ala-Trp-2'-Nal-NH₂;

H-Tyr-D-Nle-Trp-2'-Nal-NH₂;

H-Tyr-D-Nle-Trp-Trp-NH₂;

20 H-Tyr-D-Nva-Phe-Phe-NH₂;

H-Tyr-D-Ser-Phe-Phe-NH₂;

H-Tyr-D-Val-Phe-Phe-NH₂;

H-Tyr-D-Leu-Phe-Phe-NH₂;

H-Tyr-D-Ile-Phe-Phe-NH₂;

25 H-Tyr-D-Abu-Phe-Phe-NH₂'

H-Tyr-Chl-Phe-Phe-NH₂;

H-Tyr-Cle-Phe-Phe-NH₂;

H-Tyr-D-Arg-Phe-Phe-NH₂;

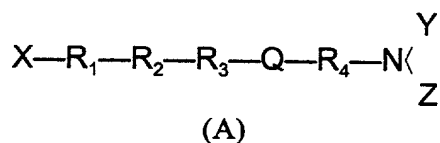
H-Tyr-D-Cys-Phe-Phe-NH₂;

30 H-Tyr-D-Thr-Phe-Phe-NH₂;

H-DMT-D-Ser-Phe-Phe-NH₂;

H-Tyr-D-Ala-Phe-Phe-OH trifluoroacetate;
 H-Tyr-D-Ala-Phe-Phg-NH₂ trifluoroacetic acid salt;
 H-Tyr-D-Arg-Phe-Hph-NH₂ bis-trifluoroacetic acid;
 H-DMT-D-Ala-Phe-Phe-NH₂ trifluoroacetic acid;
 5 H-D-DMT-D-Ala-Phe-Phe-NH₂ trifluoroacetic acid salt;
 H-Tyr-D-Ala-Phe-Hph-NH₂ trifluoroacetic acid salt;
 H-Tyr-D-Ala-Phe-Cys(Bzl)-NH₂ trifluoroacetic acid salt;
 H-Tyr-D-Arg-Hph-Phe-NH₂ bis-trifluoroacetic acid salt;
 H-Tyr-D-Arg-Phg-Phe-NH₂ bis-trifluoro acetic acid salt;
 10 H-Tyr-D-Ala-Phe-Phe-CH₂OH hydrochloride salt;
 H-Tyr-D-Ala-Hph-Phe-NH₂ trifluoroacetic acid salt;
 H-Tyr-D-Met-Phe-Phe-NH₂ trifluoroacetic acid salt;
 H-Tyr-D-Arg-Phe-D-Phe-NH₂ bis-trifluoroacetic acid salt;
 H-Tyr-D-Ala-Phg-Phe-NH₂ trifluoroacetic acid salt;
 15 H-Tyr-(D)-Ala-(D)-Phg-Phe-NH₂ trifluoroacetic acid salt;
 H-Tyr-D-Arg-Phe-Phe(pF)-NH₂ bis-trifluoroacetic acid salt;
 H-Tyr-D-Arg-Phe-D-Phe(pF)-NH₂ ditrifluoroacetic acid salt;
 H-Tyr-D-Ala-Phe-Phe(pF)-NH₂ trifluoroacetic acid salt; and
 H-Tyr-D-Ala-Phe-D-Phe(pF)-NH₂ trifluoroacetic acid salt.

- 20 16. The compound of claim 1, wherein said compound is H-Tyr-D-Ser-Phe-Phe-NH₂.
17. The compound of claim 1, wherein said compound is H-Tyr-D-Arg-Phe-Phe-NH₂.
18. A pharmaceutical composition possessing analgesic activity, comprising, in admixture with a pharmaceutically acceptable carrier, an effective amount of at least one compound having the chemical structure of formula (A):



with peripheral analgesic effect, wherein:

- 5
- a) X is selected from the group consisting of H and C₁₋₆ alkyl;
- b) Y and Z are independently selected from the group consisting of H, cyclic
aralkyl, and C₁₋₆ alkyl;
- c) R₁ is a tyrosyl residue or a 2',6'-dimethyltyrosyl residue;
- d) R₂ is an amino acid having the R-configuration, aminoisobutyric acid,
cyclopropylalanine, cyclohomoleucine or cycloleucine;
- e) R₃ is an aromatic amino acid;
- f) R₄ is an aromatic amino acid residue;
- 10 g) Q is an amide bond or an interposed amide bond mimetic;
- h) with the proviso that when:
- i) R₁ is a tyrosyl residue;
- ii) R₂ is D-alanine;
- iii) X, Y, and Z are H; and
- iv) R₃ is phenylalanine;
- then R₄ is not unsubstituted phenylalanine or phenylalanine substituted with
4NO₂ or 4N₃;
- i) with the further proviso that when:
- i) R₁ is a tyrosyl residue;
- ii) R₂ is D-alanine;
- iii) X, Y, and Z are H; and
- iv) R₄ is phenylalanine;
- then R₃ is not unsubstituted phenylalanine or phenylalanine substituted with
4NO₂;
- 20
- 25 j) with the further proviso that when:
- i) R₁ is a tyrosyl residue;
- ii) R₂ is D-alanine;
- iii) X, Y, and Z are H; and
- iv) R₄ is 1'-naphthylalanine;
- 30 then R₃ is not 1'-naphthylalanine or 2'-naphthylalanine;

- k) with the further proviso that when:
- i) R_1 is a tyrosyl residue;
 - ii) R_2 is D-alanine; and
 - iii) X, Y and Z are H,
- then both R_3 and R_4 are not tryptophan;
- l) with the further proviso that when:
- i) R_1 is a tyrosyl residue;
 - ii) R_2 is a D-amino acid with a lower alkyl or lower thioalkyl group as a side chain; and
 - iii) R_4 is a neutral amino acid,
- then R_3 is not unsubstituted phenylalanine;
- m) and wherein said compound is not selected from the group consisting of:
- H-Tyr-D-Phe-Phe-Phe-NH₂;
 - H-Tyr-D-NMePhe-Phe-Phe-NH₂;
 - H-Tyr-D-Tic-Phe-Phe-NH₂;
 - H-Tyr-Pro-Phe-Thr(Bz1)-NH₂;
 - H-Tyr-Pro-Phe-Phe-NH₂;
 - H-Tyr-Pro-Phe-Apb-NH₂;
 - H-Tyr-Pro-Phe-App-NH₂;
 - H-Tyr-Pro-Phe-Aph-NH₂; and
 - H-Tyr-Pro-Apb-Phe-NH₂;

wherein Apb is 2-amino-4-phenylbutanoic acid, App is 2-amino-5-phenylpentanoic acid and Aph is 2-amino-6-phenylhexanoic acid.

19. The pharmaceutical composition of claim 18 wherein said composition has peripheral analgesic activity and wherein said compound has a chemical structure in which X is H.
20. The pharmaceutical composition of either claim 18 or claim 19 wherein said composition has peripheral analgesic activity and wherein said compound has a chemical structure in which:
- a) R_2 is as defined in claim 18;

- b) with the proviso that when:
- i) R_1 is a tyrosyl residue;
 - ii) R_2 is D-alanine; and
 - iii) Y and Z are H;

5 then R_3 and R_4 are different and are selected from the group consisting of phenylalanine, and tryptophan.

10 21. The pharmaceutical composition of either claim 18 or claim 19 wherein said composition has peripheral analgesic activity and wherein said compound has a chemical structure in which: Q is an amide bond or an interposed amide bond mimetic of the formula Q_1-Q_2 , wherein:

- 15 a) Q_1 is selected from the group consisting of CH_2 , $CHOH$, $C=O$, $C=S$, and $CH=$; and
- b) Q_2 is selected from the group consisting of CH_2 , NH , S , SO , SO_2 , O , and $CH=$;
- c) with the proviso that when Q_1 is $CH=$, then Q_2 is $CH=$.

20 22. The pharmaceutical composition of 20 wherein said composition has peripheral analgesic activity and wherein said compound has a chemical structure in which: Q is an amide bond or an interposed amide bond mimetic of the formula Q_1-Q_2 , wherein:

- a) Q_1 is selected from the group consisting of CH_2 , $CHOH$, $C=O$, $C=S$, and $CH=$; and
- b) Q_2 is selected from the group consisting of CH_2 , NH , S , SO , SO_2 , O , and $CH=$;
- c) with the proviso that when Q_1 is $CH=$, then Q_2 is $CH=$.

25 23. The pharmaceutical composition of claim 22, wherein said composition has peripheral analgesic activity and wherein said compound has a chemical structure in which:

- a) Y and Z are H;
- b) R_2 is as defined in claim 18;
- c) R_3 is an aromatic amino acid; and

d) R_4 is an aromatic amino acid;

e) with the proviso that when:

i) R_1 is a tyrosyl residue; and

ii) R_2 is D-alanine;

5 then R_3 and R_4 are different and are selected from the group consisting of phenylalanine and tryptophan.

24. The pharmaceutical composition of either claim 18 or 19, wherein said composition has peripheral analgesic activity and wherein said compound has a chemical structure in which:

a) Y and Z are H;

b) R_2 is as defined in claim 18;

c) R_3 is an aromatic amino acid; and

d) R_4 is an aromatic amino acid;

e) with the proviso that when:

i) R_1 is a tyrosyl residue; and

ii) R_2 is D-alanine;

10
15 then R_3 and R_4 are different and are selected from the group consisting of phenylalanine and tryptophan.

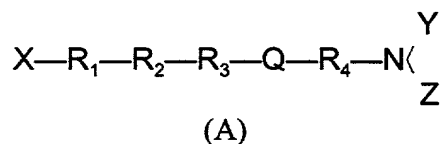
25. The pharmaceutical composition of claim 18, further comprising an effective amount of at least one other therapeutically active agent.

20 26. The pharmaceutical composition of claim 20, further comprising an effective amount of at least one other therapeutically active agent.

27. The pharmaceutical composition of claim 21, further comprising an effective amount of at least one other therapeutically active agent.

25 28. The pharmaceutical composition of claim 23, further comprising an effective amount of at least one other therapeutically active agent.

29. The pharmaceutical composition of claim 24, further comprising an effective amount of at least one other therapeutically active agent.
30. A method for the treatment of pain comprising the step of administering to a mammal in need of such treatment a pharmaceutically effective amount of at least one compound having the chemical structure of formula (A):



wherein:

- a) X is selected from the group consisting of H and C₁₋₆ alkyl;
- b) Y and Z are independently selected from the group consisting of H, cyclic aralkyl, and C₁₋₆ alkyl;
- c) R₁ is a tyrosyl residue or a 2',6'-dimethyltyrosyl residue;
- d) R₂ is an amino acid having the R-configuration, aminoisobutyric acid, cyclopropylalanine, cyclohomoleucine or cycloleucine;
- e) R₃ is an aromatic amino acid;
- f) R₄ is an aromatic amino acid residue;
- g) Q is an amide bond or an interposed amide bond mimetic;
- h) with the proviso that when:
- i) R₁ is a tyrosyl residue;
- ii) R₂ is D-alanine;
- iii) X, Y, and Z are H; and
- iv) R₃ is phenylalanine;
- then R₄ is not unsubstituted phenylalanine or phenylalanine substituted with 4NO₂ or 4N₃;
- i) with the further proviso that when:
- i) R₁ is a tyrosyl residue;
- ii) R₂ is D-alanine;

iii) X, Y, and Z are H; and

iv) R₄ is phenylalanine;

then R₃ is not unsubstituted phenylalanine or phenylalanine substituted with 4NO₂;

5 j) with the further proviso that when:

i) R₁ is a tyrosyl residue;

ii) R₂ is D-alanine;

iii) X, Y, and Z are H; and

iv) R₄ is 1'-naphthylalanine;

10 then R₃ is not 1'-naphthylalanine or 2'-naphthylalanine;

k) with the further proviso that when:

i) R₁ is a tyrosyl residue;

ii) R₂ is D-alanine; and

iii) X, Y and Z are H,

15 then both R₃ and R₄ are not tryptophan;

l) with the further proviso that when:

i) R₁ is a tyrosyl residue;

ii) R₂ is a D-amino acid with a lower alkyl or lower thioalkyl group as a side chain; and

20 iii) R₄ is a neutral amino acid,

then R₃ is not unsubstituted phenylalanine;

m) and wherein said compound is not selected from the group consisting of:

H-Tyr-D-Phe-Phe-Phe-NH₂;

H-Tyr-D-NMePhe-Phe-Phe-NH₂;

25 H-Tyr-D-Tic-Phe-Phe-NH₂;

H-Tyr-Pro-Phe-Thr(Bz1)-NH₂;

H-Tyr-Pro-Phe-Phe-NH₂;

H-Tyr-Pro-Phe-Apb-NH₂;

H-Tyr-Pro-Phe-App-NH₂;

30 H-Tyr-Pro-Phe-Aph-NH₂; and

H-Tyr-Pro-Apb-Phe-NH₂.

wherein Apb is 2-amino-4-phenylbutanoic acid, App is 2-amino-5-phenylpentanoic acid and Aph is 2-amino-6-phenylhexanoic acid.

31. The method of claim 30, wherein said compound has a chemical structure in which X is H.

32. The method of either claim 30 or claim 31, wherein said compound has a chemical structure in which:

- a) R_2 is as defined in claim 30;
- b) with the proviso that when:
 - i) R_1 is a tyrosyl residue;
 - ii) R_2 is D-alanine; and
 - iii) Y and Z are H;

then R_3 and R_4 are different and are selected from the group consisting of phenylalanine, and tryptophan.

33. The method of either claim 30 or claim 31, wherein said compound has a chemical structure in which: Q is an amide bond or an interposed amide bond mimetic of the formula Q_1-Q_2 , wherein:

- a) Q_1 is selected from the group consisting of CH_2 , $CHOH$, $C=O$, $C=S$, and $CH=$; and
- b) Q_2 is selected from the group consisting of CH_2 , NH , S , SO , SO_2 , O , and $CH=$;
- c) with the proviso that when Q_1 is $CH=$, then Q_2 is $CH=$.

34. The method of claim 32, wherein said compound has a chemical structure in which: Q is an amide bond or an interposed amide bond mimetic of the formula Q_1-Q_2 , wherein:

- a) Q_1 is selected from the group consisting of CH_2 , $CHOH$, $C=O$, $C=S$, and $CH=$; and
- b) Q_2 is selected from the group consisting of CH_2 , NH , S , SO , SO_2 , O , and $CH=$;
- c) with the proviso that when Q_1 is $CH=$, then Q_2 is $CH=$.

35. The method of 34, wherein said compound has a chemical structure in which:

- a) Y and Z are H;
- b) R₂ is as defined in claim 30;
- c) R₃ is an aromatic amino acid; and
- d) R₄ is an aromatic amino acid;
- e) with the proviso that when:
 - i) R₁ is a tyrosyl residue; and
 - ii) R₂ is D-alanine;

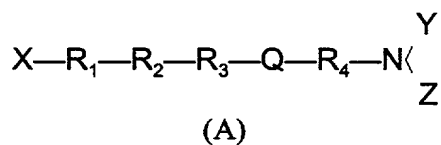
then R₃ and R₄ are different and are selected from the group consisting of phenylalanine and tryptophan.

36. The method of either claim 30 or 31, wherein said compound has a chemical structure in which:

- a) Y and Z are H;
- b) R₂ is as defined in claim 30;
- c) R₃ is an aromatic amino acid; and
- d) R₄ is an aromatic amino acid;
- e) with the proviso that when:
 - i) R₁ is a tyrosyl residue; and
 - ii) R₂ is D-alanine;

then R₃ and R₄ are different and are selected from the group consisting of phenylalanine and tryptophan.

37. A method for the treatment of pain comprising the step of administering to a mammal in need of such treatment a pharmaceutically effective amount of a pharmaceutical composition possessing analgesic activity, wherein said pharmaceutical composition comprises, in admixture with a pharmaceutically acceptable carrier, an effective amount of at least one compound having the chemical structure of formula (A):



wherein:

- 5 a) X is selected from the group consisting of H and C₁₋₆ alkyl;
- b) Y and Z are independently selected from the group consisting of H, cyclic
aralkyl, and C₁₋₆ alkyl;
- 5 c) R₁ is a tyrosyl residue or a 2',6'-dimethyltyrosyl residue;
- d) R₂ is an amino acid having the R-configuration, aminoisobutyric acid,
cyclopropylalanine, cyclohomoleucine or cycloleucine;
- e) R₃ is an aromatic amino acid;
- f) R₄ is an aromatic amino acid residue;
- 10 g) Q is an amide bond or an interposed amide bond mimetic;
- h) with the proviso that when:
- i) R₁ is a tyrosyl residue;
- ii) R₂ is D-alanine;
- iii) X, Y, and Z are H; and
- iv) R₃ is phenylalanine;
- then R₄ is not unsubstituted phenylalanine or phenylalanine substituted with
4NO₂ or 4N₃;
- i) with the further proviso that when:
- i) R₁ is a tyrosyl residue;
- ii) R₂ is D-alanine;
- iii) X, Y, and Z are H; and
- iv) R₄ is phenylalanine;
- then R₃ is not unsubstituted phenylalanine or phenylalanine substituted with
4NO₂;
- 25 j) with the further proviso that when:
- i) R₁ is a tyrosyl residue;
- ii) R₂ is D-alanine;
- iii) X, Y, and Z are H; and
- iv) R₄ is 1'-naphthylalanine;
- then R₃ is not 1'-naphthylalanine or 2'-naphthylalanine;
- 30 k) with the further proviso that when:

- i) R_1 is a tyrosyl residue;
 - ii) R_2 is D-alanine; and
 - iii) X, Y and Z are H,
- then both R_3 and R_4 are not tryptophan;

- 5 l) with the further proviso that when:
- i) R_1 is a tyrosyl residue;
 - ii) R_2 is a D-amino acid with a lower alkyl or lower thioalkyl group as a side chain; and
 - iii) R_4 is a neutral amino acid,
- 10 then R_3 is not unsubstituted phenylalanine;
- m) and wherein said compound is not selected from the group consisting of:
- H-Tyr-D-Phe-Phe-Phe-NH₂;
 - H-Tyr-D-NMePhe-Phe-Phe-NH₂;
 - H-Tyr-D-Tic-Phe-Phe-NH₂;
 - 15 H-Tyr-Pro-Phe-Thr(Bz1)-NH₂;
 - H-Tyr-Pro-Phe-Phe-NH₂;
 - H-Tyr-Pro-Phe-Apb-NH₂;
 - H-Tyr-Pro-Phe-App-NH₂;
 - H-Tyr-Pro-Phe-Aph-NH₂; and
 - 20 H-Tyr-Pro-Apb-Phe-NH₂;

wherein Apb is 2-amino-4-phenylbutanoic acid, App is 2-amino-5-phenylpentanoic acid and Aph is 2-amino-6-phenylhexanoic acid.

38. The method of claim 37, wherein said pharmaceutical composition has peripheral analgesic activity and wherein said compound has a chemical structure in which X is H.

- 25 39. The method of either claim 37 or claim 38, wherein said pharmaceutical composition has peripheral analgesic activity and wherein said compound has a chemical structure in which:
- a) R_2 is as defined in claim 37;
 - b) with the proviso that when:
 - i) R_1 is a tyrosyl residue;

ii) R_2 is D-alanine; and

iii) Y and Z are H;

then R_3 and R_4 are different and are selected from the group consisting of phenylalanine, and tryptophan.

5 40. The method of either claim 37 or claim 38, wherein said pharmaceutical composition has peripheral analgesic activity and wherein said compound has a chemical structure in which:

Q is an amide bond or an interposed amide bond mimetic of the formula Q_1-Q_2 , wherein:

a) Q_1 is selected from the group consisting of CH_2 , $CHOH$, $C=O$, $C=S$, and $CH=$; and

10 b) Q_2 is selected from the group consisting of CH_2 , NH , S , SO , SO_2 , O , and $CH=$;

c) with the proviso that when Q_1 is $CH=$, then Q_2 is $CH=$.

15 41. The method of claim 39, wherein said pharmaceutical composition has peripheral analgesic activity and wherein said compound has a chemical structure in which: Q is an amide bond or an interposed amide bond mimetic of the formula Q_1-Q_2 , wherein:

a) Q_1 is selected from the group consisting of CH_2 , $CHOH$, $C=O$, $C=S$, and $CH=$; and

b) Q_2 is selected from the group consisting of CH_2 , NH , S , SO , SO_2 , O , and $CH=$;

20 c) with the proviso that when Q_1 is $CH=$, then Q_2 is $CH=$.

25 42. The method of claim 41, wherein said pharmaceutical composition has peripheral analgesic activity and wherein said compound has a chemical structure in which:

a) Y and Z are H;

b) R_2 is as defined in claim 37;

c) R_3 is an aromatic amino acid; and

d) R_4 is an aromatic amino acid;

e) with the proviso that when:

i) R_1 is a tyrosyl residue; and

ii) R_2 is D-alanine;

then R_3 and R_4 are different and are selected from the group consisting of phenylalanine and tryptophan.

5 43. The method of either claim 37 or claim 38, wherein said pharmaceutical composition has peripheral analgesic activity and wherein said compound has a chemical structure in which:

a) Y and Z are H;

b) R_2 is as defined in claim 37;

c) R_3 is an aromatic amino acid; and

d) R_4 is an aromatic amino acid;

e) with the proviso that when:

10 i) R_1 is a tyrosyl residue; and

ii) R_2 is D-alanine;

then R_3 and R_4 are different and are selected from the group consisting of phenylalanine and tryptophan.

15 44. The method of claim 37, wherein said pharmaceutical composition further comprises an effective amount of at least one other therapeutically active agent.

45. The method of claim 39, wherein said pharmaceutical composition further comprises an effective amount of at least one other therapeutically active agent.

20 46. The method of claim 40, wherein said pharmaceutical composition further comprises an effective amount of at least one other therapeutically active agent.

47. The method of claim 42, wherein said pharmaceutical composition further comprises an effective amount of at least one other therapeutically active agent.

48. The method of claim 43, wherein said pharmaceutical composition further comprises an effective amount of at least one other therapeutically active agent.

49. A method for the treatment of pain comprising the step of administering to a mammal in need of such treatment, a pharmaceutically effective amount of the compound H-Tyr-D-Ala-Phe-Phe-NH₂ or analogues or pharmaceutically acceptable derivatives thereof.

50. The method of claim 49, wherein said analogue is selected from the group consisting of:
5 H-Tyr-D-Ala-Phe-Phe(4-NO₂)-NH₂, and H-Tyr-D-Ala-Phe-Phe(4-NO₃)-NH₂.

51. A pharmaceutical composition having analgesic activity, comprising in admixture with a pharmaceutically acceptable carrier, an effective amount of at least one peptide selected from the group consisting of:

H-Tyr-Aib-Phe-Phe-NH₂;

H-Tyr-D-Nle-Phe-Phe-NH₂;

H-Tyr-D-Ala-Phe-2'-Nal-NH₂;

H-Tyr-D-Ala-D-Phe-Phe-NH₂;

H-Tyr-D-Ala-Phe(4NO₂)-Phe(4NO₂)-NH₂;

H-Tyr-D-Ala-Phe-Tic-NH₂;

H-Tyr-D-Ala-Phe-Phe(NMe)-NH₂;

H-Tyr-D-Ala-Phe-1'-Nal-NH₂;

H-Tyr-D-Ala-Trp-Phe-NH₂;

H-Tyr-D-Ala-Phe-Trp-NH₂;

H-Tyr-∇Ala-Phe-Phe-NH₂;

20 ∇CH₂-Tyr-D-Ala-Phe-Phe-NH₂;

H-Tyr-D-Nle-Phe-Trp-NH₂;

H-Tyr-D-Nle-Phe-2'-Nal-NH₂;

H-Tyr-D-Nle-Trp-Phe-NH₂;

H-Tyr-D-Ala-Trp-2'-Nal-NH₂;

25 H-Tyr-D-Nle-Trp-2'-Nal-NH₂;

H-Tyr-D-Nle-Trp-Trp-NH₂;

H-Tyr-D-Nva-Phe-Phe-NH₂;

H-Tyr-D-Ser-Phe-Phe-NH₂;

H-Tyr-D-Val-Phe-Phe-NH₂;

H-Tyr-D-Leu-Phe-Phe-NH₂;
 H-Tyr-D-Ile-Phe-Phe-NH₂;
 H-Tyr-D-Abu-Phe-Phe-NH₂;
 H-Tyr-Chl-Phe-Phe-NH₂;
 5 H-Tyr-Cle-Phe-Phe-NH₂;
 H-Tyr-D-Arg-Phe-Phe-NH₂;
 H-Tyr-D-Cys-Phe-Phe-NH₂;
 H-Tyr-D-Thr-Phe-Phe-NH₂;
 H-DMT-D-Ser-Phe-Phe-NH₂;
 10 H-Tyr-D-Ala-Phe-Phe-OH trifluoroacetate;
 H-Tyr-D-Ala-Phe-Phg-NH₂ trifluoroacetic acid salt;
 H-Tyr-D-Arg-Phe-Hph-NH₂ bis-trifluoroacetic acid;
 H-DMT-D-Ala-Phe-Phe-NH₂ trifluoroacetic acid;
 H-D-DMT-D-Ala-Phe-Phe-NH₂ trifluoroacetic acid salt;
 15 H-Tyr-D-Ala-Phe-Hph-NH₂ trifluoroacetic acid salt;
 H-Tyr-D-Ala-Phe-Cys(Bzl)-NH₂ trifluoroacetic acid salt;
 H-Tyr-D-Arg-Hph-Phe-NH₂ bis-trifluoroacetic acid salt;
 H-Tyr-D-Arg-Phg-Phe-NH₂ bis-trifluoroacetic acid salt;
 H-Tyr-D-Ala-Phe-Phe-CH₂OH hydrochloride salt;
 20 H-Tyr-D-Ala-Hph-Phe-NH₂ trifluoroacetic acid salt;
 H-Tyr-D-Met-Phe-Phe-NH₂ trifluoroacetic acid salt;
 H-Tyr-D-Arg-Phe-D-Phe-NH₂ bis-trifluoroacetic acid salt;
 H-Tyr-D-Ala-Phg-Phe-NH₂ trifluoroacetic acid salt;
 H-Tyr-(D)-Ala-(D)-Phg-Phe-NH₂ trifluoroacetic acid salt;
 25 H-Tyr-D-Arg-Phe-Phe(pF)-NH₂ bis-trifluoroacetic acid salt;
 H-Tyr-D-Arg-Phe-D-Phe(pF)-NH₂ ditrifluoroacetic acid salt;
 H-Tyr-D-Ala-Phe-Phe(pF)-NH₂ trifluoroacetic acid salt; and
 H-Tyr-D-Ala-Phe-D-Phe(pF)-NH₂ trifluoroacetic acid salt.

30 52. The pharmaceutical composition of claim 51, wherein said peptide is
 H-Tyr-D-Nva-Phe-Phe-NH₂.

53. The pharmaceutical composition of claim 51, wherein said peptide is
H-Tyr-D-Ser-Phe-Phe-NH₂.

54. The pharmaceutical composition of claim 51, wherein said peptide is
H-Tyr-D-Arg-Phe-Phe-NH₂.

5

55. A method for the treatment of pain, comprising the step administering to a mammal in need of such treatment a pharmaceutically effective amount of a peptide selected from the group consisting of:

H-Tyr-Aib-Phe-Phe-NH₂;

H-Tyr-D-Nle-Phe-Phe-NH₂;

H-Tyr-D-Ala-Phe-2'-Nal-NH₂;

H-Tyr-D-Ala-D-Phe-Phe-NH₂;

H-Tyr-D-Ala-Phe(4NO₂)-Phe(4NO₂)-NH₂;

H-Tyr-D-Ala-Phe-Tic-NH₂;

H-Tyr-D-Ala-Phe-Phe(NMe)-NH₂;

H-Tyr-D-Ala-Phe-1'-Nal-NH₂;

H-Tyr-D-Ala-Trp-Phe-NH₂;

H-Tyr-D-Ala-Phe-Trp-NH₂;

H-Tyr-∇Ala-Phe-Phe-NH₂;

20

∇CH₂-Tyr-D-Ala-Phe-Phe-NH₂;

H-Tyr-D-Nle-Phe-Trp-NH₂;

H-Tyr-D-Nle-Phe-2'-Nal-NH₂;

H-Tyr-D-Nle-Trp-Phe-NH₂;

H-Tyr-D-Ala-Trp-2'-Nal-NH₂;

25

H-Tyr-D-Nle-Trp-2'-Nal-NH₂;

H-Tyr-D-Nle-Trp-Trp-NH₂;

H-Tyr-D-Nva-Phe-Phe-NH₂;

H-Tyr-D-Ser-Phe-Phe-NH₂;

H-Tyr-D-Val-Phe-Phe-NH₂;

30

H-Tyr-D-Leu-Phe-Phe-NH₂;

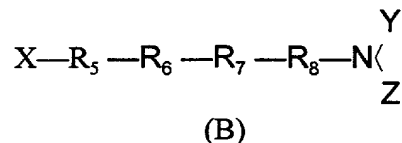
- H-Tyr-D-Ile-Phe-Phe-NH₂;
 H-Tyr-D-Abu-Phe-Phe-NH₂;
 H-Tyr-Chl-Phe-Phe-NH₂;
 H-Tyr-Cle-Phe-Phe-NH₂;
 5 H-Tyr-D-Arg-Phe-Phe-NH₂;
 H-Tyr-D-Cys-Phe-Phe-NH₂;
 H-Tyr-D-Thr-Phe-Phe-NH₂;
 H-DMT-D-Ser-Phe-Phe-NH₂;
 H-Tyr-D-Ala-Phe-Phe-OH trifluoroacetate;
 10 H-Tyr-D-Ala-Phe-Phg-NH₂ trifluoroacetic acid salt;
 H-Tyr-D-Arg-Phe-Hph-NH₂ bis-trifluoroacetic acid;
 H-DMT-D-Ala-Phe-Phe-NH₂ trifluoroacetic acid;
 H-D-DMT-D-Ala-Phe-Phe-NH₂ trifluoroacetic acid salt;
 H-Tyr-D-Ala-Phe-Hph-NH₂ trifluoroacetic acid salt;
 15 H-Tyr-D-Ala-Phe-Cys(Bzl)-NH₂ trifluoroacetic acid salt;
 H-Tyr-D-Arg-Hph-Phe-NH₂ bis-trifluoroacetic acid salt;
 H-Tyr-D-Arg-Phg-Phe-NH₂ bis-trifluoro acetic acid salt;
 H-Tyr-D-Ala-Phe-Phe-CH₂OH hydrochloride salt;
 H-Tyr-D-Ala-Hph-Phe-NH₂ trifluoroacetic acid salt;
 20 H-Tyr-D-Met-Phe-Phe-NH₂ trifluoroacetic acid salt;
 H-Tyr-D-Arg-Phe-D-Phe-NH₂ bis-trifluoroacetic acid salt;
 H-Tyr-D-Ala-Phg-Phe-NH₂ trifluoroacetic acid salt;
 H-Tyr-(D)-Ala-(D)-Phg-Phe-NH₂ trifluoroacetic acid salt;
 H-Tyr-D-Arg-Phe-Phe(pF)-NH₂ bis-trifluoroacetic acid salt;
 25 H-Tyr-D-Arg-Phe-D-Phe(pF)-NH₂ ditrifluoroacetic acid salt;
 H-Tyr-D-Ala-Phe-Phe(pF)-NH₂ trifluoroacetic acid salt; and
 H-Tyr-D-Ala-Phe-D-Phe(pF)-NH₂ trifluoroacetic acid salt.

56. The method of claim 55, wherein said peptide is H-Tyr-D-Nva-Phe-Phe-NH₂.

57. The method of claim 55, wherein said peptide is H-Tyr-D-Ser-Phe-Phe-NH₂.

58. The method of claim 55, wherein said peptide is H-Tyr-D-Arg-Phe-Phe-NH₂.

59. A compound of formula (B):



and salts thereof wherein,

- a) R₅ is Tyr or 2',6'-dimethyltyrosine, or an analog or derivative thereof;
 - b) R₆ is D-Ala or D-Arg;
 - c) R₇ is Phe(pF);
 - d) R₈ is Phe or Phe(pF);
 - e) X is H or C₁₋₆ alkyl; and
 - f) Y and Z are independently H, aralkyl or C₁₋₆ alkyl.
60. The compound according to claim 59, wherein R₆ is D-Ala.
61. The compound according to claim 59, wherein R₆ is D-Arg.
62. The compound according to claim 59, R₈ is Phe.
63. The compound according to claim 62, wherein R₆ is D-Ala.
64. The compound according to claim 62, wherein R₆ is D-Arg.
65. The compound according to any one of claims 59-64 wherein X is H, and Y and Z are both H.
66. The compound according to claim 59, wherein said compound is selected from the group consisting of:

H-Tyr-D-Ala-Phe(pF)-Phe(pF)-NH₂; and
H-Tyr-D-Ala-Phe(pF)-Phe-NH₂.

67. The compound H-Tyr-D-Ala-Phe(pF)-Phe-NH₂.
68. The compound according to claim 59, wherein said compound is selected from the group consisting of:
5 H-Tyr-D-Arg-Phe(pF)-Phe(pF)-NH₂ and
H-Tyr-D-Arg-Phe(pF)-Phe-NH₂.
69. The compound H-Tyr-D-Arg-Phe(pF)-Phe-NH₂.
70. A pharmaceutical composition comprising a compound according to any one of claims 59-64, or 66-69 in admixture with a pharmaceutically acceptable carrier.
71. A pharmaceutical composition comprising a compound according to claim 65, in admixture with a pharmaceutically acceptable carrier.
72. A method for the treatment of pain comprising, administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound according to any one of claims 59-64 or 66-69.
15
73. The method of claim 72, wherein said peptides are administered to a human at a dosage of between 0.05 mg/kg and 20 mg/kg.
74. The method of claim 73, wherein said peptides are administered at a dosage of between 0.1 mg/kg and 1.0 mg/kg.
- 20 75. A method for the treatment of pain comprising, administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound according to claim 65.

76. The method of claim 75, wherein said peptides are administered to a human at a dosage of between 0.05 mg/kg and 20 mg/kg.
77. The method of claim 75, wherein said peptides are administered at a dosage of between 0.1 mg/kg and 1.0 mg/kg.